UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,977	10/02/2003	Jack Nguyen	19049-005001 / 4905	9061

20985 7590 02/07/2008
FISH & RICHARDSON, PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
02/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/677,977	NGUYEN ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,11-16,45-48,50-54 and 56-66* is/are pending in the application.

4a) Of the above claim(s) *2* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,9,11-16,45-48,50-54 and 56-636* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the decision on the petition (3/16/2007), all claims on the petitioned groups would be examined in the application. Restriction/election with respect to the groups no longer exists. However, the restriction with respect to the species i.e., target-caspase 3 and protease-granzyme B is maintained.

Status of Claims

Claims 1-7, 9, 11-16, 45-48, 50-54 and 56-66 are pending and under examination in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9, 11-16, 45-48, 50-54 and 56-66, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention.

The claims recite for a method of identifying a protease that cleaves a substrate sequence comprising producing a library of mutein protease sequences with each member having N mutations relative to the wild type scaffold whererin N is 1-20.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

The disclosure at the time of filing does not describe the huge scope of the claimed components of the broad claimed method steps. The claimed method steps recite only a method of producing a library of a peptide, measuring the activity of the two members of the library and identifying at least one mutein. The claims do not only cover a huge scope of the method steps but also a huge scope of the enzyme and its mutants in a library. It does not provide direction as to the kind of enzyme that can be mutagenized, the location of N-mutations(residues) and/or number of mutations in any of the recited enzymes. The method steps do not provide any distinguishing features of the broad claimed method steps and components employed in the method. The disclosure at page 3 recites a diverse number of

mutations made in the enzyme scaffold. It lists the different protease enzymes, pathology and target. However, a laundry list disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967). The illustrative Examples, which allegedly provide a detail description of the invention, are drawn to specific method steps employing a single, defined compound species. The specification discloses that even the specific method steps employing a specific type of protease, serine proteinases, the enzymes exhibit different substrate specificities. Some enzymes have an extended interaction site with the substrate whereas others have a specificity restricted to the P1 substrate residue. Three residues which form the catalytic triad is essential in the catalytic process i.e. His 57, Asp 102 and Ser 195. It seems likely, given the early stage of the field, that more roles exist [for caspase, a cys protease]. Caspases and caspase regulators involved in these processes may be missed in screens that focus strictly on T-5 cell death related phenotypes. Thus, molecules that possess caspase or caspase regulatory activity may not have been identified yet. For the cysteine proteases, the amino acids selected to be modified are

less well described. Serine proteases, family of proteases, do not have well-defined pockets for substrate recognition. One therefore cannot immediately envisage from the single species the genus as claimed, as based on the disclosure above, given the early stage of the field in which applicants are working in.

ENABLEMENT

Claims 1, 3-7, 9, 11-16, 45-48, 50-54 and 56-66, as amended, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include:

(1) the breadth of the claims,
(2) the nature of the invention,
(3) the state of the prior art,
(4) the level of one of ordinary skill;
(5) the level of predictability in the art,
(6) the amount of direction provided by the inventor,
(7) the existence of working examples, and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, (U.S.P.Q. 2d 1400 (CAFC 1988).

1). The specification fails to give adequate direction and guidance in how to readily go about determining the mutations that can be done to a scaffold of any protease to produce a library of muteins.

2). The specification failed to provide working examples for any of the numerous and different type of mutations in the protease or the library of muteins of such broad scope using the broad method steps.

3). The breadth of the claims encompasses a large diversity of mutant enzyme, the kind of enzyme involve in mutations, the number of residues that undergo mutations, the predetermination of the sites of variations of the amino acids involve in the variation. It is well known in the art, that it is often difficult to know where insertions in the enzyme for mutations can be done without deleteriously affecting the enzyme-specificity substrate function or its global structure. The diversity of the inserts is not easily estimated for any kind of enzyme peptide.

4). The state of the prior art is such that techniques are specifically applied for a predetermined enzyme/substrate and muteins thereof in view of the high specificity reaction of enzyme/substrate.

5). The art is inherently unpredictable because it is not possible to predict which predetermined (variations) of amino acids in different mammalian protease would result in the desired mutant with a desired pharmacologic activity. Bornscheuer et al (Curr. Opin. in Chem. Biol.) states at page 137, col. 2 that depending on the purpose of the mutagenesis, amino acid substitutions are often selected by sequence comparison 16, with homologous sequences. The results have to be carefully interpreted, however, because minor sequence changes by a single point-mutation may cause significant structural disturbance. See further the discussion above. Also, see the prior art discussion as to the unpredictability in the art e.g., Harris et al (PNAS) reference e.g., at page 7754 and Legendre (J. Mol. Biol.) at e.g., page 90, paragraph bridging col. 1 and col. 2.

6). Because the art is unpredictable, applicants' specification reasonably would not have assured persons skilled in the art that the numerous (undefined) variables of the claim would result in mutations having a pharmacologic activity without undue experimentation. Applicants do not adequately enable persons skilled in the art to readily determine such. Applicants need not guarantee the success of the full scope of the claimed invention. However, skilled artisans are provided with little assurance of success.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9, 11-16, 45-48, 50-54 and 56-66, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Step b) is unclear as to the activity of the protease being measured. There seems to be a lack of nexus between the preamble and step c of the claimed method. The preamble implicitly recites treatment of pathology by protease cleavage. Step c recites identifying the mutein protease relative to the cleavage activity to that of the wild-type protease. It is not clear as to the N mutations of the numerous different proteases comprised in a library, given no structure or fingerprint of the wild type protease to form a mutein library. Is the mutations made from a single protease or a combinations of different proteases? Step (b) is confusing as to whether an activity relates to step c "increased cleavage activity". The claimed

"and/or" is unclear as to the conditions when the increased cleavage activity is separately or in combination determined with the alleged specificity. (Claim 1).

2. Claim 7 reference to "the mammalian protease scaffold" lacks antecedent basis of support from the base claim, at least it is unclear whether it refers to the wild-type or mutants.

3. Claims 7, 9, for example, are unclear as from which "among" the e.g., protease can selection be made. Furthermore, the term "derived" is unclear as to how and where said derivation is done for the different recited proteases.

4. Claim 12 is indefinite in the recitation of caspase as the target. The base claim does not recite for an enzyme target.

5. Claim 16 steps d) and e) are unclear as to how two or more members of the protease library identified with increased cleavage activity is provided. It is also unclear whether two simultaneous mutations are being done on the same or different libraries. This claim appears to broaden the base claim.

6. Claims 45 and 57 are unclear as to whether in repeating the steps a new library is being created. Furthermore, the base claim does not recite for a selectivity activity.

7. Claim 46 is unclear as to which "earlier iteration of the method" is being referred thereto.

8. Claim 47 is unclear as to the "corresponding" wild type protease i.e., in what sense it corresponds to the wild-type. This claim does not seem to further limit the base claim which already contains this limitation "relative to the wild-type."

9. For claim 53, see the rejections under 1, 3 and 4 above.

10. Claim 63 is incomplete for omitting essential structural cooperative relationships of elements and essential steps, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the steps between steps (a) and (b). It is not clear as to how step (b) can occur given no step for providing a substrate or a step by which an enzyme cleaves a substrate sequence.

11. Claim 63, step © "wild-type mammalian protease scaffold" is inconsistent with the wild-type scaffold sequence of a ***human*** protease as recited in step (a). Also, it is not clear as to the difference between identifying a protease mutein having an "increased" cleavage activity from an "altered" activity, especially in the absence of positive differentiating steps between the two.

12. Claim 64 recitation of "wild-type mammalian protease scaffold" is inconsistent and at odds with the base claim 63 recitation of a "human protease scaffold". This appears to be

duplicative and repetitive since the identifying step for an altered protease is not definitively recited.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 9, 11-16, 45-48, 50-54 and 56-66, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over either Harris et al (The Journal of Biological Chemistry)(I) or (Current Opinion in Chemical Biology(II) alone, or Harris (I or II) in view of Bianchi et al (Biopolymers).

Harris et al discloses at page 27364, a method of identifying optimal substrate specificity for proteases as granyzme B that allows for the identification of in vivo substrates in the process. The method comprises using the combinatorial methods of synthetic substrate libraries and substrate-phage display for an optimum substrate for granzyme B that spans over six subsites. Granzyme B proteolysis was shown to be highly dependent on the length and sequence of the

substrate. Supporting the role of granyzme B preferred substrate sequence matches the activation sites of caspases 3 and 7 that is consistent with the role of granzyme B in the activation of these caspases during apoptosis. Many caspase substrates contain granzyme B cleavage site and are potential granzyme B targets. Harris at page 27364 discloses construction of granzyme B variants of R192A and R192E. Harris (II) throughout the article, at e.g., pages 127-129, basically discloses the same method as Harris (I).

Harris(I), for example, does not disclose a combinatorial library mutant for the enzyme granzyme B. However, Bianchi at page 112, col.1 and col. 2 discloses that the use of peptide libraries in protease drug discovery has often been limited to substrate optimization, rather than to inhibitor (i.e., enzyme) optimization. Bianchi discloses the numerous advantages in the used of the combinatorial library of enzymes. It would have been obvious to one having ordinary skill in the art at the time the invention was made to make a library of the enzyme (inhibitor) in the method of Harris replacing the library of substrate as taught by Bianchi. The numerous advantages provided by Bianchi and the beneficial effect of changing from a substrate library to an enzyme library would motivate one to make said changes. Furthermore, the disclosure of Harris of the

different variants of granzyme could read or would lead one to a combinatorial library of said enzyme.

Claims 16, 45-46 and 53 are obvious over the disclosure of Harris of the known iterative process of phage display method.

Claims 1, 2-7, 9, 11-16, 45-48, 50-54 and 56-66, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Koltermann et al (US 2004/0072276) in view of Waugh et al (Nature Structure Biology).

Koltermann et al discloses throughout the patent at e.g.,:

> [0016] (1) a method for generating sequence-specific proteases with target substrate specificities which comprises the following steps; [0017] (a) providing a population of proteases comprised of variants of one first protease (claim 1)or of variants or chimeras of two or more first proteases,(claim 53) said first proteases having a substrate specificity for a particular amino acid sequence of a first peptide substrate; [0018] (b) contacting said population of proteases with one or more second substrates, comprising at least one specific amino acid sequence resembling the amino acid sequence of the target peptide substrate but being not present within the first peptide substrate; and [0019] (c) selecting one or more protease variants from the population of proteases provided in step (a) having specificity for said specific amino acid sequence of the second substrates provided in step (b) under conditions that allow identification of proteases that recognize and hydrolyze preferably said specific one amino acid sequence within the second substrates; [0024] The identification and selection of proteases that have evolved towards the target specificity is done by screening for catalytic activities on different peptide substrates, either by screening for increased affinity, or by using two substrates in comparison, or by using unspecific peptides as competitors, or by using intermediate peptide substrates..

Koltermann discloses at e.g., paragraph:

> [0059] ...any protease can be used as first protease. Preferably, an endoprotease is used as first protease. It is preferred that the protease belongs to the group of proteases consisting of Serine proteases, Cysteine proteases, Aspartic proteases, and Metalloproteases. First proteases are characterized by their ability to recognize and hydrolyze peptide substrates with a certain qualitative and quantitative specificity. First proteases can have specificity in the same range as the specificity of the protease that is to be generated. Examples for proteases with relatively high specificities are TEV protease, HIV-1 protease, BAR1 protease, Factor Xa, Thrombin, tissue-type plasminogen activator, Kex2 protease, TVMV-protease, RSV protease, MuLV protease... Alternatively, the first proteases have a lower specificity than the specificity of the protease that is to be generated. As an extreme example of the latter, proteases with very low sequence specificity are employed, for example proteases such as Papain, Trypsin, Chymotrypsin, Subtilisin, SET (trypsin-like serine protease from Streptomyces erythraeus), Elastase, Cathepsin G or Chymase.
>
> See further the Examples, pages 12-14.

Koltermann does not disclose that the enzyme used in the method is granzyme B, (the elected species). However, Waugh discloses at page 762 that Granzymes are a vial component of the cytotoxic lymphocyte's ability to induce apoptosis, contributing to rapid cell death of a tumor or virally infected target cell by the cleavage of downstream substrates and the activating cleavage of caspases. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use granzyme as the enzyme in the method of

Koltermann as taught by Waugh. One would be motivated to use granzyme for the advantage taught by Waugh above i.e., rapid cell death of a tumor cell.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw
January 30, 2008